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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	19

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/872,527	Guo
Examiner	**Group Art Unit**
Marianne DiBrino	1644

X Responsive to communication(s) filed on *Jul 6, 2000*

This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

X Claim(s) *1-4, 6-10, 12, 13, 33-38, 49-52, 57, 63, and 66-102* is/are pending in the applicat

Of the above, claim(s) *73, 74, and 76-85* is/are withdrawn from consideration

Claim(s) _____ is/are allowed.

X Claim(s) *1-4, 6-10, 12, 13, 33-38, 49-52, 57, 63, 66-72, 75, and 86-102* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s) _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's amendment, filed 7/6/00 (Paper No. 18), is acknowledged and has been entered.

Newly added claims 73, 74, 76-85 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species of the elected Group I.

Claims 1-4, 6-10, 12, 13, 33-38, 49-52, 57, 63, 66-72, 75 and 86-102 are presently being examined.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

3. Upon reconsideration of the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999; the following rejection is set forth herein.

Claims 1-4, 6-10, 12, 13, 33-38, 49-52, 57, 63, 66-72, 75 and 86-102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed immunogenic composition, or method of curing or treating a disease using said composition, said composition comprising an isolated autologous target diseased cell and a bridge molecule capable of stimulating T cell activation comprising one or more binding sites for one or more costimulatory molecules on the surface of T cells.

The instant claims encompass a composition comprising any autologous target diseased cell and any bridge molecule capable of stimulating T cell activation comprising one or more binding sites for one or more costimulatory molecules on

the surface of said T cells. There is insufficient disclosure in the specification on said composition.

The specification discloses (on pages 9 and 10 at lines 23-27 and 10-13) that said binding sites can be directed towards 4-1BB, ICAM-1, ICAM-2, ICAM-3, LFA-1, LFA-2, VLA-1 VCAM-1, B7-1, B7-2 and other cell adhesion proteins and other cell surface proteins which can activate T cell costimulatory pathways through T cell surface proteins. The specification further discloses (on page 10 at lines 17-20) that said bridge molecules include, but are not limited to, bispecific monoclonal antibodies, fusion proteins, organic polymers and hybrids of chemical and biochemical materials and in addition (on page 11 at lines 11-27 and page 12 at lines 1-7) may be antigens, fatty acids, lipids, steroids and sugars that can stimulate or costimulate effector cells' function to destroy target cells, or may be one of the multitude of CD molecules listed on pages 11 and 12. The specification discloses bispecific antibodies CD28:gp55, CD28:gp95 and CD28:gp210 (figures and Example 6.2). The specification further discloses CD28:gp55 armed HEPA 1-6 (hepatoma tumor cells), EL-4 (lymphoma cells) or SMCC-1 (colon carcinoma cells) (Examples 6.2-6.7). The specification also discloses EL-4 tumor cell armed -Bi-Mab anti-gp115:anti-4-1BB (4-1BB is a glycoprotein expressed on primed T CD4+ and CD8+ T cells) (Example 6.8).

The specification discloses (on page 10 at lines 26-27 and on page 11 at lines 1-10) that the antigen on the target cell serving as an anchor for the bridge molecule can be any molecule, including but not limited to, proteins, glycoproteins, lipids, glycolipids, phospholipids, lipid aggregates, steroids, and carbohydrate groups such as disaccharides, oligosaccharides and polysaccharides, and further, may be transferrin receptor, LDL receptor, gp55, gp95, gp210, ICAM-1, ICAM-2, collagen and fibronectin receptors, transferrin receptors, Fc receptor and cytokine receptors.

The specification discloses that the source of the tumor cells can include among others liver cancer, hepatocellular carcinoma, lung cancer, gastric cancer, colorectal carcinoma, renal carcinoma, head and neck cancers, sarcoma, lymphoma, leukemia, brain tumors, osteosarcoma, blade carcinoma, my[e]loma, melanoma, breast cancer, prostate cancer, ovarian cancer and pancreas carcinoma (page 8 at lines 18-27 and page 9 at line 1).

The specification also discloses in vitro data on human hepatocellular carcinoma (Example 6.9).

The instant claims encompass bridge molecules that bind to costimulatory molecules other than CD28 and 4-1BB. The instant claims also encompass bridge molecules that are not limited to bispecific monoclonal antibodies and tumor cells that are not limited to hepatocellular carcinoma cells and colon carcinoma cells. There is insufficient disclosure in the specification on said composition and the components of said composition.

4. Claims 33-38, 49-51, 57 and 63 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of reducing growth of HEPA 1-6 hepatoma, or EL-4 lymphoma or SMCC-1 colon carcinoma tumor cells in mice, does not reasonably provide enablement for a method of curing cancer in mice or in any other mammal patient, including humans, nor for a method of treatment of tumors that are not hepatoma, lymphoma or colon carcinoma in any mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification does not disclose how to use the instant invention for the curing of patient mammals of diseased cells. The claimed methods encompass methods of curing a human patient suffering from cancer. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass methods for curing cancer in vivo in humans. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be used for curing cancer in vivo in humans. The specification discloses no working examples with regards to the use of the instant invention for the curing of disease in vivo in humans or in any mammal.

The instant application discloses (on pages 37-39 and 40-42) use of the invention to cause hepatoma tumor cell regression in mice and to cause tumor regression of EL-4 lymphoma and SMCC-1 colon carcinoma in mice, respectively.

It has been art-recognized experience that for any novel therapy, the transition from the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Chatterjee et al., Cancer Immunol. Immunother., 1994; see Introduction). Results obtained under controlled conditions and in inbred animals often differ from the clinical response obtained in patients. This applies in particular to strategies based on immune responses, including strategies drawn to cancer therapy. Concerning animal models, the response of animals to chemotherapy, radiation and surgery is generally predictive of their effect in human patients (Osband et al., Immunol. Today 11: 193-195, 1990). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy in vivo. Tumors are classified as

immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

For these reasons, it is not clear that reliance on the invention to reduce tumor growth in mice of three tumor cell types accurately reflects the relative efficacy of the claimed therapeutic strategy in curing cancer in humans or in treating any mammal including humans for tumors that are not hepatoma, lymphoma or carcinoma.

There is insufficient guidance in the specification as to how to practice the method of the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Applicant's arguments filed 7/6/00 have been fully considered but they are not persuasive.

Reducing growth of diseased cells is not the equivalent of "curing" cancer.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 1-4, 6, 8-10, 12, 13, 52, and newly added claims 66-67, 69, 70-72 and 86 stand rejected under 35 U.S.C. 102(a) as being anticipated by Shi et al (Proc. Amer. Assoc. Cancer Res. March 1996, Volume 37, page 480, Abstract No. 3278) for the reasons of record in Paper No. 16, mailed 1/20/00.

Applicant's arguments have been considered but are not persuasive. The inventive entity of the Shi et al reference is different from the inventive entity of the instant application and the Applicant has not provided a Katz type declaration under 37 CFR 132. Although Applicant has stated that he is the sole inventor of the claims in the instant application, Applicant has not provided a signed statement explaining the nature of the contribution to the published reference, of the other authors of the Shi et al reference.

The reference teachings anticipate the claimed invention.

7. Claim 7 stands rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Shi et al (Proc. Amer. Assoc. Cancer Res. March 1996, Volume 37, page 480, Abstract No. 3278) as evidenced by Rink (Int. Arch. Allergy Immunol. 1996, Vol. 111, pages 199-209) the reasons of record in Paper No. 16, mailed 1/20/00.

Applicants arguments have been considered but are not persuasive. The inventive entity of the Shi et al reference is different from the inventive entity of the instant application and the Applicant has not provided a Katz type declaration under 37 CFR 132. Although Applicant has stated that he is the sole inventor of the claims in the instant application, Applicant has not provided a signed statement explaining the nature of the contribution to the published reference, of the other authors of the Shi et al reference.

The reference teachings anticipate the claimed invention.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-4, 6-10, 12, 13, 33-38, 49-52, 57, 63, and newly added claims 66, 67, 72 and 86-102 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,484,596 in view of Wang et al (Int. J. Cancer, Vol. 51, pages 962-967, 1992) and Vanky et al (Semin. Cancer Biol., Vol. 2(1), pages 55-62, 1991) both in view of, Renner et al (Science, Vol. 264, page 833, 1994) or Bohlen (Blood, vol. 82, pages 1803-1812, 1993), admissions in the specification, Darlington et al (JNCL, Vol. 64, page 809, 1980), Chapoval et al (J. Immunol., Vol. 155, pages 1296-1303, 1995) and Krummel et al (J Exp. Med., Vol. 182, pages 459-465, 1995).

U.S. Patent No. 5,484,596 discloses using irradiated tumor cells as a vaccine, (especially Abstract).

U.S. Patent No. 5,484,596 does not disclose cytokine-induced elevation of MHC class I and ICAM-1 on tumor cells ex vivo nor does it disclose bispecific antibodies that bind to CD28 and to a tumor-associated antigen like gp55 and it does not provide motivation for bridging tumor cells to CTL's via CD28

Wang et al teach cytokine-induced elevation of MHC class I and ICAM-1 (CD54) expression on tumor cells treated ex vivo with TNF-α and IFN-γ (page 962, second column). Such induction is taught to result in tumor cells that interact more readily with autologous lymphocytes and induce CTLs that even lyse untreated tumor cells. Vanky et al teach that in vitro treatment of tumor cells with TNF-α and IFN-γ induces expression of MHC class I antigens and ICAM-1 and that expression of class I MHC antigens is necessary for recognition of the tumor cells by autologous lymphocytes that lyse the tumor cells. Wang et al teaches breast, kidney, ovarian, lung and stomach carcinomas.

Renner et al teach that bispecific monoclonal antibodies that bind to CD28 and to tumor-associated antigens (CD30) in order to "target human T cells to the tumor cells in vivo." The exact identity of the antibody that binds to the target cell (for the elected species gp55) does not appear to be critical to the invention, see page 10, lines 25-27 of the instant specification. Assuming *arguendo* that use of antibodies recognizing gp55 from HEPA 1-6 is a critical feature of the invention, page 29 of the specification admits that HEPA 1-6 cells were known in the prior art. Darlington et al also teach such hepatoma cells. Page 32, lines 10-15 admit that methods of making monoclonal antibodies were known and page 33, lines 4-7 admit that methods of making bispecific antibodies were known.

Bohlen et al also teach targeting of T cells to tumor cells using bispecific antibodies comprising a ligan for CD28 (especially Abstract) and page 1810 indicates that optimal responses may be maintained by the administration of CD28 antibodies to ensure proliferation and stimulation of tumor-specific T cells.

Chapoval et al teach that bispecific antibodies that bridge T cells and tumor cells trigger activation of T cells and retarget such activated T cells to tumor cells resulting in lysis of tumor cells (especially Abstract and pages 1301-1302).

Krummel et al teach that CD28 is the "major costimulatory molecule for proliferation of T cells" and that antibody engagement of CD28 on T cells augments T cell responses and can supply costimulation to T cells encountering APCs deficient in costimulation (HEPA 1-6 cells are deficient in antigen presentation because they lack MHC class I expression, see pages 29-30 of the instant specification).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have treated tumor cells such as the cells of the 5,484,596 patent with TNF-α or Ifn-γ to increase levels of MHC class I and ICAM-1 (CD54) as taught by Wang et al and Vanky et al and to arm said tumor cells with a bispecific antibody comprising a portion specific for a tumor antigen on the surface of said tumor cells and further comprising a portion specific for CD28 such as the bispecific antibodies of Renner et al, Bohlen et al and Chapoval et al, to be administered in vivo, given the teaching of Wang et al and Vanky et al that ex vivo cytokine treatment of tumor cells increases levels of class I and ICAM-1 and the teachings of Renner et al, Bohlen et al and Chapoval et al that bispecific antibodies are effective for bridging T cells and tumor cells and for inducing T cell responses to tumor cells, and particularly given the teaching of Wang et al that in vitro treatment of tumor cells with the TNF-α or Ifn-γ cytokines induces CTLs that even lyse untreated tumor cells.

One of ordinary skill in the art would have been motivated to do this in order to induce and/or increase an in vivo response of the cellular arm of the immune system, i.e., of CTL that would be capable of destroying tumor cells.

Claims 89-92, 94-98, 100 and 101 are included in the instant rejection because the tumor cells recited in these claims are obvious variants of tumor cells known to cause disease and they were known by the skilled artisan at the art at the time the invention was made.

Applicant's arguments have been considered, but are not deemed persuasive for the reasons of record in Papers No. 14 and 16, mailed 7/14/99 and 1/20/00, respectively, and for the reasons stated below.

With further regard to Applicant's comments on Applicant's Declaration under 37 C.F.R. 1.132, in particular item 4, Applicant is reminded that declarations must set forth facts, not merely conclusions. In re Pike et al., 84 USPQ 235. And concerning Applicant's comments on concentration dependence (page 7 of Paper No. 14, second paragraph), it follows that if a higher concentration of antibody is administered, that individual bispecific antibodies will bind to one cell (tumor cell)

or another (T cell) rather than one individual bispecific antibody binding to both a tumor cell and a T cell. With regard to Applicant's further comments in the same paragraph of Paper No. 14, the data in Figure 6 of said Declaration is not a side-by-side comparison. If the combined references in the instant rejection were to add cytokine treated T cells in addition to bispecific antibody armed (and cytokine treated) tumor cells which express higher levels of class I MHC and ICAM-1, one would expect to get an enhanced immune response due to the added activated T cells. In addition, Wang et al teach cytokine-induced elevation of MHC class I molecules in tumor cells (especially second full paragraph on page 962, and the Materials and Methods section). These tumor cells then were then subsequently used to initiate MLTC. With regard to Applicant's Declaration under 37 C.F.R. 1.132, in particular items 7-9 and 5, Applicant has not repeated the method of Wang et al with Applicant's tumor cell lines because as stated above, Wang et al did not treat mixtures of tumor cells and T cells with cytokines as did Applicant.

In addition, said Figure 6 provides no explanation of whether the components were administered simultaneously or sequentially and what the components actually were. For instance, how does the legend marked "Tumor + BsAb + T cell" differ from "Complex +T cell"? In item 8 of Applicant's Declaration, Applicant states immunization with " a mixture of cytokine treated tumor and lymph[o]cyte cells with CD28 BiMabs, or with injection of tumor cells followed by intravenous or intraperitoneal BiMab administration". Applicant states in item 9 of said Declaration that Figure 2 of said Declaration shows the desirability of not including functional T cells in the vaccine, however, Figure 6 appears to show the highest activation when functional T cells are included in the vaccine. With regard to Applicant's statement that the open transition phrase "comprising" in the instant claims does not exclude the co-administration of T cells, it is pointed out, however, that the specification does not appear to support a limitation of co-administration of T cells. Such a limitation, if added to the instant claims would constitute new matter.

With regard to Applicant's argument in the same paragraph of Applicant's amendment (paragraph 2 page 7), concerning the requirement that the composition or method be useful for treating a patient, the instant claims are not restricted to "non or weakly immunogenic tumors" and said composition would also be useful for tumors that are immunogenic because the immune response would be further boosted. The scope of the purported unexpected results is not commensurate with the scope of the claimed invention.

10. Claims 68, 69, 70 and 71 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,484,596 as applied to claims 1-4, 6-10, 12, 13, 33-38, 49-52, 63, and newly added claims 66, 67, 72 and 86-102 above in view of Wang et al (Int. J. Cancer, Vol. 51, pages 962-967, 1992) and Vanky et al (Semin. Cancer Biol., Vol. 2(1), pages 55-62, 1991) both in view of, Renner et al (Science, Vol. 264, page 833, 1994) or Bohlen (Blood, vol. 82, pages 1803-1812, 1993), admissions in the specification, Darlington et al (JNCL, Vol. 64, page 809, 1980), Chapoval et al (J. Immunol., Vol. 155, pages 1296-1303, 1995) and Krummel et al (J Exp. Med., Vol. 182, pages 459-465, 1995) and further in view of Albeda et al (FASEB J. 8: 504-512, 5/1994), Ward et al (Ther. Immunol. 1: 165-171, 1994) and Shi et al (Proc. Amer. Assoc. Cancer Res. March 1996, Volume 37, page 480, Abstract No. 3278).

U.S. Patent 5,484,596, Wang et al,Vanky et al, Renner et al, Bohlen et al, admissions in the specification, Darlington et al, Chapoval et al and Krummel et al have all been discussed supra.

The combined references do not teach a method comprising using an autologous target diseased cell that expresses ICAM-2 or VCAM-1 at higher levels than in a said cell in a diseased mammal.

Albeda et al and Ward et al teach ICAM-2 and VCAM-1 are molecules known to skilled artisans at the time the invention was made which are involved in cell adhesion and costimulation in inflammatory reactions (especially Table 1 of Albeda et al and Table 1 of Ward et al).

Shi et al teach B7 (e.g., B7.1 and B7.2) is a costimulatory molecule.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have increased levels of ICAM-2 or VCAM-1 of Albeda et al or Ward et al or the B7 of Shi et al on the tumor cells of the combined invention instead of inducing expression of ICAM-1 because these molecules are other costimulatory molecules known in the art at the time the invention was made.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to boost an immune response to said tumor cells.

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-4, 6-10, 12, 13, 33-38, 49-52, 57, 63 and newly added claims 66-72, 75 and 86-102 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 10, 11, 7-9, of copending Application No. 09/216,604. Although the conflicting claims are not identical, they are not patentably distinct from each other because it would have been obvious to remove unbound bridge molecule (claim 6 in '604), it would be obvious to use the costimulatory molecules listed in instant claim 4, it would have been obvious to treat target diseased cells with the cytokines listed in instant claim 8 which are known in the art for the purpose stated, it would have been obvious to use the binding sites or antigens listed in the instant claims which were known in the art, a pharmaceutical composition used for treating a human patient would first be tested in an animal, it would have been obvious to increase costimulatory molecules in vitro with cytokines or in vivo. Therefore, the two sets of claims would have been prima facie obvious to one of ordinary skill in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 1-4, 6-10, 12, 13, and newly added claims 66-72, 75 and 86-102 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of copending Application No. 09/216,062. Although the conflicting claims are not identical, they are not patentably distinct from each other because it would have been obvious to remove

unbound bridge molecule (claim 6 in '062), it would be obvious to use the costimulatory molecules listed in instant claims 4 and 66-71 of '527, it would have been obvious to use the binding sites or antigens listed in the instant claims and the target diseased cells listed in the instant claim, which were known in the art and it would have been prima facie obvious to purify, isolate or enrich said composition for administration. Therefore, the two sets of claims would have been prima facie obvious to one of ordinary skill in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. No claim is allowed.

15. This action is made NON-final.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
September 28, 2000

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1300~~ 1640